Remarks

Claims 21, 23-25, 27-34 and 51-54 are pending in the subject application. By this Amendment, Applicants have canceled claims 27-28 and 32-54 and amended claims 21 and 23. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed and previously presented. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 21, 23-25 and 29-31 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 21, 23-25, 27-34 and 51-54 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action indicates it is not clear if the blood sample or cytapheresis sample initially contains gamma delta T lymphocytes, and the method is intended to enrich the proportion of gamma delta T lymphocytes within the sample; or if the biological preparation may contain any mononuclear cells, and the method is intended to involve transdifferentiation of various (non-gamma delta T lymphocytes) mononuclear cells into gamma delta T lymphocytes Applicants respectfully assert that the claims as filed are definite.

"[T]he definiteness of the language employed must be analyzed-not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971). Applicants respectfully assert that the biological preparation would be recognized, as assessed and interpreted from the perspective of one skilled in the art, to contain mononuclear cells that include, within the mononuclear cell population, γδ T lymphocytes. For example:

- "Gamma delta T cells normally account for 1 to 5% of peripheral blood lymphocytes in a healthy individual (human, monkey)" (paragraph [002] of the application as published);
- "A peripheral blood cell preparation generally contains from 30 to 70% of T or B lymphocytes, from 5 to 15% of NK cells and from 1 to 5% of γδ T cells" (paragraph [0023] of the application as published);
- the term "transdifferentiation" is never used in the application whereas the term "proliferation" appears in numerous locations of the as-filed application;

- "In so far a typical biological preparation comprises at the outset less than 10% of gamma delta T cells, usually less than 5% gamma delta T cells, a preparation of 100 millions cells typically contains from 1 to 5 million gamma delta T cells. [...] Moreover, while the starting preparation contains only about 1 to 5% of gamma delta T cells, the compositions obtained by the method according to the invention are composed of more than 80%, even more than 90%, of gamma delta T cells" (paragraph [0029] of the application as published); and
- The Examples clearly discuss and demonstrate the expansion and induced proliferation of gamma delta T-cells from blood samples or cytapheresis samples.

Therefore, it is submitted that the biological preparation of claim 21 initially contains γδ T cells and that this would have been recognized by those skilled in the art at the time the invention was made. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 21, 23-25, 27-34, 51-54 are rejected under 35 U.S.C. § 103(a) as obvious over Belmant *et al.* (U.S. Patent No. 6,660,723), in view of Skea *et al.* (2001), Garcia *et al.* (1998) and Valeri (1976). Claims 21, 23-25, 27-34, 51-54 are rejected under 35 U.S.C. § 103(a) as obvious over Espinosa *et al.* (2001), in view of Skea *et al.* (2001), Garcia *et al.* (1998) and Valeri (1976). Applicants respectfully assert that the claimed invention is not obvious over the cited references.

In both rejections, the Office Action asserts that the concentration of IL-2 to be added to the cell culture would have been easily determined as a matter of "routine optimization" since IL-2 was recognized to be a result effective variable that would have been optimized by those skilled in the art. The Office Action also argues that such a finding is supported by the data disclosed in Garcia *et al.* (Fig. 2). Applicants respectfully submit that the data derived from Garcia *et al.* would not have been so interpreted by those skilled in the art. Figure 2 reports results obtained with γδ T cell clones, that is to say, pure γδ T cell populations. Such populations are not the same as those recited within the claims (a population of mononuclear cells of which 1-5% are γδ T cells). Thus, it is respectfully submitted that the teaching of Garcia *et al.* does not relate to the same cell population and the given concentration is only relevant for a pure γδ T cell population.

Even assuming that one skilled in the art would look to Garcia *et al.* for pertinent teachings regarding the use of IL-2 for the stimulation of γδ T-cells, Garcia *et al.* clearly establishes that one

skilled in the art would have looked to optimize IL-2 levels at concentrations far greater than those claimed herein (150-500 U/mL). As noted in a previous response, the Board of Patent Appeals and the predecessor of the Court of Appeals for the Federal Circuit (the Court of Customs and Patent Appeals) have held that while it may generally be a matter of obviousness for the skilled artisan to determine the optimum value within an already disclosed range, *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980), it would not have been obvious for one of ordinary skill in the art to find an optimum value that is far outside the range taught by the prior art. *See In re Sebek*, 465 F.2d 904, 907 (C.C.P.A. 1972). *See also, e.g., Ex parte Atkinson*, BPAI Appeal 2007-3900 ("optimization of a known result-effective variable in a given range is generally obvious only when it is reasonably expected that an improvement will arise in that range") (reversing Examiner's optimization-based obviousness rejection; internal citation omitted).

As indicated by Figure 2, γδ T-cell proliferation induced by IL-2 is insignificant at levels less than 100 ng/mL (~1630 U/mL) and far lower than that stimulated by IL-15 under the same culture conditions. Indeed, the figure would appear to indicate that increasing IL-2 levels above the 100 ng/mL (1630 U/mL) disclosed within the reference would further increase γδ T-cell proliferation. Thus, the "optimal amount" of IL-2 that one skilled in the art would have sought to use, based upon the teachings of Garcia *et al.*, is far outside the range claimed in this matter and the claimed range of IL-2 concentrations cannot be considered obvious in view of the cited references.

Additionally, and contrary to the assertion made in the Office Action, γδ proliferation does not appear to have been significantly induced at the 10 ng /mL (~163 U of IL-2; see HF.2, 12G12 and DG.SFP6). Significant proliferation was only observed at 100 ng/mL (~1630 U of IL-2). Moreover, Garcia *et al.* argues that IL-2 is not a good cytokine to obtain γδ T cell proliferation: "*Moreover, we found that IL-15 was a more potent inducer of gd T cell proliferation than IL-2 (Fig. 2)*" (see page 4324, column 2, last sentence). Applicants also note that the Office Action argues that Belmant teach increasing IL-2 levels to 100 U/mL by the additive effect of two (2) 50 U/mL additions of IL-2 to the cultured γδ T-cells. Applicants submit that this assertion, on the part of the Patent Office, ignores the fact that IL-2 is bound to receptors on the surface of γδ T-cells and consumed during proliferation of the cells. Thus, the assertion made in the Office Action is not accurate and reconsideration of this position is respectfully requested.

The Office Action also argues that Skea *et al.* would indicate to those skilled in the art that cells could be maintained at densities of around 1 x 10^5 cells/mL. As noted in a previous response, and the declaration of Samuel Salot, Skea *et al.* clearly indicate that maximum proliferation of the cells would have been expected to have occurred within 7 days after the start of culturing the cells. Thus, it is unclear that one skilled in the art would have had a reasonable expectation of success in practicing the claimed methods since one skilled in the art, on the basis of the cited prior art, would not have had a reasonable expectation of success in culturing the cells for the period of time recited within the claims. Accordingly reconsideration and withdrawal of the obviousness rejections of record is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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